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09/787,879	03/22/2001	Takuya Watanabe	2553US0P	9847

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,879	WATANABE ET AL.	
	Examiner	Art Unit	
	Basi N Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 8/25/03 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-28 is/are pending in the application.

4a) Of the above claim(s) 10-14,16,18,19 and 22-28 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-9,15,17,20 and 21 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 22 March 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group I (Claims 1-9, 15, 17, 20, 21) pertaining to the protein of SEQ ID NO:1 encoded by the nucleic acid of SEQ ID NO:3) on 8/25/03, is acknowledged. The traversal is on the ground(s) that the compounds of the identified Group I and methods of use of such, identified as Groups VII-XI are sufficiently related so as to unduly burden the Examiner in making a search. Applicants arguments have been fully considered but not found persuasive. A search of groups I and VIII-XI would not be co-extensive particularly with regard to the literature search. Further the first appearing product, method of making and method of using are grouped together in Group I, as is appropriate for the invention being examined. An examination of the materially different, patentably distinct inventions in a single application would constitute a serious undue burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Further Applicant is required to cancel/amend elected claims pertaining to non-elected invention, ie. relating to SEQ ID NOs: 2 and 4.

Objections

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 or 35 U.S.C. 371 as follows: It is not clear if the applicant is claiming priority to PCT/JP99/05366 under 35 U.S.C. 119 or 35 U.S.C. 371.

Further an application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Appropriate correction is required.

3. Acknowledgment is made of applicant's claim for foreign priority based on an application 10-279535, filed in Japan on 01/10/1998. It is noted, however, that applicant has not filed a an English translation of the application.

Appropriate correction is required.

4. ***Sequence Rules Compliance***

This application fails to comply with the sequence rules, 37 CFR 1.821-1.825. Nucleotide and polypeptide sequences must be identified with the corresponding SEQ ID NO. Title 37, Code of Federal Regulations, Section 1.821 states "reference must be made to the sequence by use of the assigned identifier", the identifier being SEQ ID NO. Figure 2 contains two sets of sequences, and only one has been identified by SEQ ID NO:. All sequences in Figure 2 must be identified by their corresponding SEQ ID NO:. Correction is required.

Claim Rejection, 35 U.S.C. 112

5. Claims 1-9, 15, 17 and 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 are indefinite because it is not clear when an amino acid sequence is "substantially identical" to an amino acid sequence represented by SEQ ID NO:1 and how such is determined so as to allow the metes and bounds of the claim to be determined. It is not clear when a sequence is substantially identical, as compared to when it is not substantially identical, so as to allow the metes and bounds of the claim to be determined. The term "substantially" is not defined by the claim, the specification does

not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Further it is not clear which parameter is being used to determine identity, e.g. molecular weight, primary structure etc. It is suggested, to overcome the rejection, the terms "substantially" be omitted from the claim and replaced with a specific % identity.

Claims 3 and 15 are indefinite because it is not clear when a peptide is considered a partial peptide so as to allow the metes and bounds of the claim to be determined. Examiner has interpreted "peptide" as being a natural or synthetic compound as containing two or more amino acids linked by the carboxyl group of one amino acid and the amino group of another. Therefore a "partial peptide" is considered by the examiner to mean any part of a peptide which is less than two amino acid, said part can be an atom or even an ion. Further claim 3 is objected to because it is broader in scope than the base claim. The "partial peptide" encompasses more compounds than the base claim.

Claim 15 is indefinite because the method steps do not achieve the goal of determining a ligand for the G protein coupled receptor (GPCR). An acceptable method claim must contain three sections: 1) a preamble, 2) method steps that clearly define what is to be done in each step, and 3) a conclusion that what was stated in the preamble was achieved (the method does not contain specific assay steps and a statement how and when the goal of the claim is achieved). The method must contain steps disclosing how the ligand for the GPCR is determined.

Claim 20 is indefinite because "highly stringent" hybridization conditions are not specified. The metes and bounds of the group of sequences that would meet the limitations of the claim depend upon the precise conditions under which hybridizations

were performed including wash conditions. Since the hybridization and wash conditions dictate which nucleic acid sequences remain specifically bound to the claimed polynucleotide the metes and bounds of the claims cannot be determined without the disclosure of said conditions.

Claims 4-9, 17 and 21 are rejected for depending upon an indefinite base (or intermediate) claim and fail to resolve the issues raised above.

Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-9, 15, 17 and 20-21 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

A "specific utility" is a utility that is specific to the subject matter claimed, as opposed to a "general utility" that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world"

context of use are not substantial utilities. A "well established utility" is a utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. A "well established utility" must also be specific and substantial as well as credible.

Based on the record, there is not a "well established utility" for the claimed invention. Applicant has asserted utilities for the specifically claimed invention of claims 1-9, 15, 17 and 20-21. Claims are drawn to: a) GPCR protein/partial peptide which is substantially identical to the polypeptide of SEQ ID NO:1; b) GPCR polynucleotide encoding the GPCR claimed in a); c) method of producing the GPCR of a); d)method of determining the ligand of the GPCR of a); e) kit comprising the GPCR of a), f) polynucleotide which hybridizes to the polynucleotide of b). The claims encompasses fragments and variants of the protein/nucleic acids disclosed in SEQ ID NO:1 and 3, as well a proteins/nucleic acids which may be completely unrelated, structurally and functionally. The claims also encompass use of said unrelated proteins/nucleic acids or fragments and variants thereof.

The specification discloses the GPCR of SEQ ID NO:1 is encoded by the polynucleotide of SEQ ID NO:3. The receptor protein is disclosed to have about 30% homology with MAS (page 47, last paragraph), a GPCR. There is no experimental data provided on the functionality of the claimed GPCR. Based solely on the homology data to MAS and the general classification into the superfamily of GPCRs, the specification discloses the claimed receptor is useful for preventing and/or treating diseases associated with dysfunction of the central function for example, mental disease comprising anxiety, schizophrenia, manic-depressive psychosis, dementia, mental retardation and dyskinesis",

page 48, first paragraph. There is no disclosure of the specific activity of claimed GPCR or how to assay for said activity. Further no ligands that bind or activate said protein are disclosed. In light of the specification the skilled artisan can not come to any conclusions as to the function of claimed GPCR.

The utility of claimed protein cannot be implicated solely from homology to the proteins known in the art because the art does not provide teaching stating that all protein disclosed have the same activity, same effects, the same ligands and are involved in the same disease states (discussed later). On the contaray, Young (US Patent 5,320,941) discloses a polypeptide which has 25.1% query match with SEQ ID NO: and encodes a onhcogene. In light of the specification and art the skilled artisan can not come to any conclusions as to the function of protein of instant invention. There is no disclosure provided within the instant specification on what specific function the protein of SEQ ID NO:1 possesses, or how to specifically assay for such, ligands that bind, promoters that activate; nor are any cell types/tissues disclosed that specifically express this protein; nor are any disease states disclosed that are directly related to said protein dysfunction.

The specification fails to disclose, what disease is associated with claimed receptor dysfunction or what drugs effect a specific claimed receptor function. The claims, specification, nor prior art disclose the ligand that binds claimed receptor, the activity associated with claimed receptor, how the activity is modulated, and how the modulation or activity is determined using specific assay steps. The claimed receptor may have utility in the future, when it has been further characterized (e.g. its dysfunction or function correlated with a disease state) and its ligand characterized. The inclusion

in the family of G protein coupled receptors (GPCR) does not constitute either a specific and substantial asserted utility or a well established utility for that particular GPCR or protein. This is analogous to all proteins or GPCRs can be used as protein markers on a gel.

Specification discloses claimed receptors are useful in screening but the specification does not disclose what claimed receptor specifically regulates and what specific disease, claimed receptor, is a target for. What would be the use of using the claimed receptor on a panel for drug screening? The receptor has no known ligand or known function. How would one use the compounds that interacted with said orphan receptors? The specification provides a diverse list of disease states that may be involved in claimed receptor dysfunction. It is unpredictable what ligands will bind to orphan receptors, and further the functional effects of ligand binding may remain uncertain even after extensive experimentation. What is the utility for a ligand, in many cases with no known function, that binds to a receptor of no known function? The ordinary artisan can only speculate on the utility for the ligand and receptor. A utility to orphan receptor cannot be assigned without knowledge of what disease is associated with claimed receptor dysfunction or what drugs/ligands effect a specific claimed receptor function. The superfamily of G-protein-coupled receptors are highly divergent in their effects and include receptors for hormones, neurotransmitters, paracrine substances, inflammatory mediators, certain proteinases, taste and odorant molecules, and even photons and calcium ions. Members of a sub-family of G-protein-coupled receptors are also highly divergent in their effects, as highlighted by Murdoch et al (Blood, Volume 95, No.10, pages 3032-3043, 2000), in the discussion of cytokine G-protein-coupled

receptors. The utility of claimed receptor cannot be implicated solely from homology to known G-protein coupled receptors or their protein domains because the art does not provide teaching stating that all members of family of G-protein coupled receptors must have the same effects, the same ligands and be involved in the same disease states, the art discloses evidence to the contrary. Specification has used protein domains/homology are predictive as to the activity of the protein. Murdoch discloses the superfamily of G-protein-coupled receptors are highly divergent in their effects and include receptors for hormones, neurotransmitters, paracrine substances, inflammatory mediators, certain proteinases, taste and odorant molecules, and even photons and calcium ions. Members of a sub-family of G-protein-coupled receptors are also highly divergent in their effects, as highlighted by Murdoch et al, in the discussion of cytokine G-protein-coupled receptors. The utility of claimed receptor cannot be implicated solely from homology to known G-protein coupled receptors or their protein domains because the art does not provide teaching stating that all members of family of G-protein coupled receptors must have the same effects, the same ligands and be involved in the same disease states, the art discloses evidence to the contrary. Further, the G-protein that interacts with the claimed orphan receptor and is required for the signal transduction activity is unknown. Further, the G-protein that interacts with the claimed orphan receptor and is required for the signal transduction activity is unknown. Watson (The G-Protein Linked receptor Facts Book, pages 2-6 and 223-230, 1994) states "It has therefore not been possible to identify consensus amino acid sequences that confer G-protein specificity, and thus G-protein interactions cannot be predicted from the primary amino acid sequence". Therefore the disclosure of Watson predicts, using the primary structure of the G-protein coupled

receptor the skilled artisan cannot predict its associated G-protein or its ligand. G-protein coupled receptors are highly specialized and ligand specific proteins. The superfamily of seven transmembrane domain G-protein coupled receptors are specialized proteins designed for chemical recognition of ligands and subsequent transduction of information encoded in those ligands to the machinery of the cell, and the G-protein coupled receptors interact with alkaloids, biogenic amines, peptides, glycoprotein hormones, light and odorents (Terry Kenakin, Pharmacological Reviews, Vol. 48, No.3, pages 413-462), see page 413. Kenakin also states, "To achieve information transfer, the ability to bind ligands to a recognition domain and allosterically transmit the presence of that ligand to an intracellular domain appears to be a specialized feature of 7TM receptors. The very properties that define receptors as such also impart unique protein behaviors to receptors, and these behaviors, in turn, affect drug activity", page 414, column 1, second paragraph. Bork (Nature Genetics, Vol 18, pages 313-318, 1998) provide a review article disclosing the problems of using homology detection methods to assigning function to related members of a family. Bork discloses: a) "While current homology detection methods can cope with data flow, the identification, verification and annotation of functional features need to be drastically improved", page 313, column 1, Abstract, b) there are two bottle necks that need to be overcome en route to efficient functional predictions from protein sequences, i.e, "First, there is the lack of a widely accepted, robust and continuously updated suite of sequence analysis methods integrated into coherent and efficient prediction system. Second, there is considerable 'noise' in the presentation of experimental information, leading to insufficient or erroneous function assignment in sequence databases", page 313, column 1, third paragraph, c) "In-depth analysis of

protein sequences often results in functional predictions not attained in the original studies", page 313, column 2, last paragraph, d) "However, more often than not, it is clear that the cellular role of the protein in question differs from that of the detected homologue(s) and there is currently no automatic means to establish how much functional information can be legitimately transferred by analogy from homologue to the query", page 315, column 2, last paragraph, e) pertaining to predictions of protein function, "Do not simply transfer functional information from the best hit. The best hit is frequently hypothetical or poorly annotated; other hits with similar or even lower scores may be more informative; even the best hit may have a different function", while "many proteins are multi functional; assignment of a single function, which is still common in genome projects, results in loss of information and outright errors" and "It is typical that the general function of a protein can be identified easily but the prediction of substrate specificity is unwarranted; for example, many permeases of different specificity show approximately the same level of similarity to each other", page 316. Karp (Bioinformatics, Vol 14, No.9, pages 753-754, 1998) has disclosed the problems of using functional prediction based on homology analysis. Karp states, a) "Although we know the accuracy with which sequence homologs can be determined, we know little about the accuracy of the overall process of assigning function by homology, page 753, column 2, second paragraph, b) "We have more faith in the correctness of those sequences whose functions we determined experimentally, rather than through computational means, page 753, column 2, last paragraph, c) "research is required to estimate the error rate of functional annotation by different methods of computational sequence analysis", page 754, column 2, last paragraph. Bork (Current Opinion in Structural Biology, Vol 8,

pages 331-332, 1998), discusses the problems with deriving biological knowledge from genomic sequences and states, "structural similarity does not lead to iron-clad functional predictions" page 331, column 2 last paragraph, "Structural similarity does not necessarily mean a common evolutionary origin" page 332, column 1, second paragraph, and "Today, what we predict from sequences is at best fragmentary and qualitative", page 332, column 2, second paragraph. Therefore, references discussed above disclose the unpredictability of assigning a function to a particular protein based on homology, especially one that belongs to the family of GPCRs which have very different ligand specificity and functions.

It can be argued the claimed receptor polypeptides/polynucleotides are useful as tools as reagents and targets as a molecular target in the diagnosis and treatment of claimed GPCR mediated disorders. All members of the GPCR protein family have a utility in selectively screening of candidate drugs that target GPCRs. However, for a utility to be "well-established" it must be specific, substantial. In this case, as all receptors are in some combination useful in selectively screening of candidate drugs that target GPCRs and in toxicology testing. However, the particulars of screening of candidate drugs, that target claimed GPCR, and in toxicology testing are not disclosed in the instant specification. Neither the candidate drugs or toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to SEQ ID NO:1 and 3. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed,

the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed protein for screening compounds that are a target for claimed GPCR is only useful in the sense that the information that is gained from the assay and is dependent on the effect it has on the protein, and says nothing with regard to each individual member of the GPCR family. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicants' individual GPCR is affected by a test compound in an assay for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed method of using claimed GPCR has no "well-established" use. The artisan is required to perform further experimentation on the claimed GPCR itself in order to determine to what "use" any information regarding this protein could be put.

With regard to diagnosis of disease, in order for a polynucleotide or protein to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed GPCR and a disease or disorder. The presence of claimed GPCR in tissue is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed GPCR and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed GPCR to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that

the claimed GPCR is either present only in, e.g. cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of claimed GPCR as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed GPCR and any disease or disorder and the lack of any correlation between the claimed GPCR with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Further, GPCR to which the polypeptide encoded by the polynucleotide of SEQ ID NO:3 belongs is a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. The diversity of the GPCRs has already been described. Without some common biological activity for the family members, a new member would not have a specific or substantial utility when relying

only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities which may be related to tissue distribution but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for drug screening, toxicology testing and diagnosis, is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use.

Without knowing a biological significance of the claimed GPCR, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible "real world" manner based on the diversity of biological activities possessed by the GPCR family. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In*

re Brana, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The assertion that the claimed invention has utility in drug screening, drug development and disease diagnosis, do not meet the standards for a specific, substantial or well-established utility for reasons set forth above. None of the utilities identified have been demonstrated to be specific to the polypeptide of SEQ ID NO:1 . One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the polypeptide SEQ ID NO:1 nor the polynucleotide of SEQ ID NO:3. Applicant has failed with respect to claimed GPCR, has not described the family of GPCRs in enough detail to show, by a preponderance of the evidence, that the polypeptide of SEQ ID NO:1 or the polynucleotide of SEQ ID NO:3 or fragments and variants thereof has any substantial use. The record shows that the family of proteins having GPCR domains is diverse, and has such a broad definition, that a "common utility" cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention.

The use of the claimed invention for toxicology testing, drug discovery, and disease diagnosis are not substantial utilities. The question at issue is whether or not the broad general assertion that the claimed GPCR might be used for some diagnostic application in the absence of a disclosure of which diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

The prior rejection under § 101 followed *Brenner v. Manson*. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. A rejection under § 112, first paragraph, may be affirmed on

the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967). Further since the claimed GPCR has no utility, methods of its use are also rejected for lack of utility.

7. Claims 1-9, 15, 17 and 21-21 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed protein (SEQ ID NO:1), polynucleotide (SEQ ID NO:3), fragments, variants thereof. Further experimentation is necessary to attribute a utility to the claimed polypeptides and fragments thereof.

The claims fail to disclose how to use the claimed invention for the reasons given above (lack of utility). Further the claims are drawn to an orphan GPCR. The claimed nucleic acid encodes an orphan receptor whose activity, associated G-protein and activating ligands have not been disclosed. The claims nor the specification disclose what specific biological activity is associated with the claimed GPCR. There is no disclosure of the specific compounds that are activated in the signal transduction pathway or what ligand is capable of binding to the polypeptide encoded by the claimed polynucleotide, so as to disclose a specific function for the claimed polynucleotide. Therefore nucleic acid encoding unrelated and inactive proteins are encompassed by the claims. The specification does not disclose how to produce active variants or how to use inactive ones. There is no disclosure of how to assay variants since the natural ligand and function of the claimed invention is unknown.

The complex nature of GPCRs and the unpredictability of assigning a function to a receptor with no known ligand or function is described in the rejection under 35 USC § 101 and 35 USC § 112, 1st paragraph, see the teachings of Murdoch, Watson, Kenakin, Karp and Bork, disclosed above.

Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Further, many of the polypeptides, encoded by the nucleic acids which hybridize to the polynucleotide encoding the GPCR of claim 1, may be inactive or unrelated to the claimed receptor of instant invention (SEQ ID NO:1). Further many of the substantially identical GPCRs encompassed by the claims or their partial peptides , may be inactive or unrelated to the claimed receptor of instant invention (SEQ ID NO:1). The specification does not disclose a utility for or how to use said inactive or unrelated polypeptides encoded by claimed nucleic acid molecule. The claimed nucleic acid encodes an orphan receptor whose activity, associated G-protein and activating ligands have not been disclosed. The claims nor the specification disclose what specific biological activity is associated with the claimed GPCR. There is no disclosure of how to assay variants identified by the hybridization procedure, or even the substantially identical GPCR, since the natural ligand and function of the claimed invention is unknown. Specific stringent hybridization conditions have not been provided. Therefore the hybridization conditions recited in the claim do not constitute a meaningful structural limitation.

Pertaining to claims 20 and 21, instant fact pattern closely resembles that in Ex parte Maizel, 27 USPQ2d 1662 (BPAI 1992). In Ex parte Maizel, the claimed invention was directed to compounds which were defined in terms of function rather than sequence (i.e., "biologically functional equivalents"). The only disclosed compound in both the instant case and in Ex parte Maizel was the full length, naturally occurring protein. The Board found that there was no reasonable correlation between the scope of exclusive right desired by Appellant and the scope of enablement set forth in the patent application. Even though Appellant in Ex parte Maizel urged that the biologically functional equivalents would consist of proteins having amino acid substitutions wherein the substituted amino acids have similar hydrophobicity and charge characteristics such that the substitutions are "conservative" and do not modify the basic functional equivalents of the protein, the Board found that the specification did not support such a definition, and that the claims encompassed an unduly broad number of compounds. Such is the instant situation. Clearly, a single disclosed sequence does not support claims to any nucleic acid hybridizing to same, given the lack of guidance regarding what sequences would hybridize specifically to polynucleotide encoding the GPCR substantially identical to that in claim 1, and not other, related sequences. Further, many of the polypeptides encoded by the nucleic acids isolated by hybridization will be unrelated to the protein of instant invention, being devoid of its characteristic structural and functional features. Said unrelated polypeptides may be produced by frame shift in the coding sequence of the nucleotide, for example. Other polypeptides may be truncated, for example. Due to the large quantity of experimentation necessary to identify the polypeptides with the structural and functional features of instant invention, the lack of direction/guidance

presented in the specification regarding the identification, purification, isolation and characterization of said polypeptides, the unpredictability of the effects of mutation on the structure and function of proteins (since mutations of SEQ ID NO:1 are also encompassed by the claim), and the breadth of the claim which fail to recite meaningful structural and functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope.

Furthermore, the specification does not reasonably provide enablement for the scope of use of nucleotides encoding polypeptides comprising fragments of claimed receptor. The claims also encompass variants of the polynucleotide encoding the polypeptide of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification discloses a polynucleotide which encodes claimed receptor. The specification does not teach how to make functional claimed receptor variants or to use inactive variants. The prior art teaches that amino acid substitutions produce unpredictable results in a structurally related protein. Furthermore, neither the specification nor the prior art provide any guidance as to which amino acids could be altered, nor does the specification provide any guidance as to how the skilled artisan could use inactive claimed receptor variants. Therefore, it would require undue experimentation to practice this invention as claimed, because the skilled artisan would have no reasonable expectation that claimed receptor variants could be used for any purpose. Further the nucleic acids that comprise fragments or variants of SEQ ID NO:3 or encode fragments or variants of the polypeptide of SEQ ID NO:1 may not specifically

hybridize to the polynucleotide of SEQ ID NO:3 or to the polynucleotide that encodes the polypeptide of SEQ ID NO:1. Applicant has not disclosed how to use said nucleic acids that do not specifically hybridize the polynucleotide of SEQ ID NO:3 or to the polynucleotide that encodes the polypeptide of SEQ ID NO:1. Many of the nucleic acids encoded by the nucleic acid encoding the polypeptide of SEQ ID NO:1 would not hybridize to the polynucleotide of SEQ ID NO:3 due to the degeneracy of the genetic code, or frame shift. Further the specification does not disclose how to use nucleic acids that comprise fragments or variants of SEQ ID NO:3 or encode fragments or variants of the polypeptide of SEQ ID NO:1 without functional activity.

Therefore, pertaining to variants comprising partial peptides/fragments of proteins substantially identical to SEQ ID NO:1 or nucleic acid encoding partial peptides/fragments of the polypeptide substantially identical to SEQ ID NO:1, due to the large quantity of experimentation necessary to identify the nucleic acids encoding polypeptides with the structural and functional features of instant orphan GPCR (the critical feature of the invention is not disclosed, ie structure and function relationship), the lack of direction/guidance presented in the specification regarding the identification, purification, isolation, characterization and assaying (no specific assay disclosed which measures claimed orphan receptor activity) of claimed invention, the unpredictability of the effects of mutation on the structure and function of proteins (since mutations of SEQ ID NO:1 and 3 are also encompassed by the claim), construction of active variants (no disclosure of which amino acids can be mutated and still provide active protein) and the breadth of the claim which fail to recite structural (except for the nucleic acid of SEQ ID NO:3, encoding the polypeptide of SEQ ID NO:1) and functional limitations containing

critical feature of the invention, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope.For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention. A review of *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the whether undue experimentation would be required to use the claimed invention. As is evidence in the discussions *supra*, each of these factors has been carefully considered in the instant grounds of rejection, and it is maintained that undue experimentation would be required by the skilled artisan to use the instant invention. Further since the claimed GPCR has no utility, methods of its use are also rejected under 35 USC § 112, 1st paragraph

Claim Rejection 35 USC § 112, 1st paragraph (Written Description)

8. Claims 1-5, 7-9, 15,17 and 20-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are drawn to: a) GPCR protein/partial peptide which is substantially identical to the polypeptide of SEQ ID NO:1; b) GPCR polynucleotide encoding the GPCR claimed in a); c) metthod of producing the GPCR of a); d)method of determining the

ligand of the GPCR of a); e) kit comprising the GPCR of a), f) polynucleotide which hybridizes to the polynucleotide of b). The claims encompasses fragments and variants of the protein/nucleic acids disclosed in SEQ ID NO:1 and 3, as well a proteins/nucleic acids which may be completely unrelated, structually and functionally. The claims also encompass use of said unrealted proteins/nucleic acids or fragments and variants thereof. The common function of the polynucleotide (SEQ ID NO:3) encoding the polypeptide (SEQ ID NO:1), which is based upon a common property or critical technical feature of the genus claimed is not disclosed. The claims, as written, encompass nucleic acid encoding polypeptides which vary substantially in length and also in amino acid composition. The instant disclosure of a polynucleotide of SEQ ID NO:3 encoding the polypeptide of SEQ ID NO:1 does not adequately describe the scope of the use of the claimed genus, which encompasses a substantial variety of subgenera including polynucleotide encoding full-length proteins, comprising fragments of SEQ ID NO:3 or encoding polypeptides which are substantially identical to the SEQ ID NO:1, chimeric proteins, fusion proteins, variants and polynucleotides which hybridize to the nucleic acid of claim 4, which may encode polypeptides completely, unrelated functionally to the polypeptide of SEQ ID NO:1. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of

the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. For example, what regions and fragments of the claimed GPCR contain a definitive structural feature required for protein function? The specification proposes to discover other members of the genus by using screening assays and techniques involving probes, primers, hybridization. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed. No identifying characteristic or property of the instant polypeptides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific polypeptide and nucleotide sequences and the inability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe, enable and use the genus as broadly claimed. The skilled artisan cannot envision the detailed chemical structure of the encompassed proteins and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. It is

acknowledged that the skill of the artisan in the molecular biology art is high. However, in the current instance, **there is no clear evidence of activity possessed by the claimed genus of polypeptides, the critical special technical feature of the polypeptides or how the critical special technical feature encompassed by the genus claimed relates to function.** Because of the lack of guidance in the prior art and current application, one skilled in the art could not predict if the variants containing fragments of claimed GPCR have the same activity as the protein disclosed in SEQ ID NO:1, since no activity is disclosed, or if they contain the domain(s) of SEQ ID NO:1, containing the critical special technical feature of the claimed GPCR, since no critical special technical feature is disclosed.

Pertaining to partial peptides or the polynucleotides encoding partial polypeptides which are substantially identical to SEQ ID NO:1, the specification does not disclose the critical feature which must be contained in said partial peptides or polypeptides which is required for activity. The skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly

allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115). Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid or polypeptide is itself is required. See *Fibers v. Revel*, 25 USPQ d. 1601 at 1606 (CAFC 1993) and *Amen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Therefore the specification fails to disclose the activity of the claimed genus of polypeptides, the critical special technical feature of the polypeptides or how the critical special technical feature encompassed by the fragments and variants of claimed GPCR relates to function. Similarly pertaining to nucleic acids which hybridize to the polynucleotide of claim 4,

under unclearly defined hybridization conditions, what is the special technical feature encompassed by said nucleic acids and how do they relate to function.

The claims encompass proteins/nucleic acids which are structurally and functionally unrelated to the protein/nucleic acid of SEQ ID NO:1 and 3. Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. Although claims recite "G protein coupled receptor", there is no disclosure of the specific activity of claimed GPCR and how it is specifically assayed The specification nor claims disclose the specific activity of the "orphan receptor" of instant invention nor a description of the conserved regions which are critical to the structure and function of the genus claimed.

There is no disclosure of the signal transduction activity transduced by the claimed genus or orphan receptors, the nature of the signal or specific signal transduction pathway. The claimed nucleic acid encodes an orphan receptor whose activity, associated G-protein and activating ligands have not been disclosed. The specification nor prior art provide a specific assay for the genus claimed. Nucleic acids comprising "substantially identical" claimed GPCRs may be completely unrelated to the GPCR of SEQ ID NO:1 encoding the polypeptide of SEQ ID NO:3. The complexity of assigning a function and membership into a the genus of orphan receptor claimed is highlighted in the references of Murdoch, Watson, Bork and Karp, disclosed above. Assigning function by homology is unpredictable by using the complete sequence of an orphan receptor, let alone using a fragment which may not have any domains related to a particular function. The claims

nor the specification disclose what specific biological activity is associated with the claimed GPCR or the special technical feature encompassed by specific fragments associated with a specific activity of the claimed genus. The superfamily of seven transmembrane domain G-protein coupled receptors are specialized proteins designed for chemical recognition of ligands and subsequent transduction of information encoded in those ligands to the machinery of the cell, and the G-protein coupled receptors interact with many diverse compounds having diverse effects(See Terry Kenakin, Ref A). Kenakin states, "To achieve information transfer, the ability to bind ligands to a recognition domain and allosterically transmit the presence of that ligand to an intracellular domain appears to be a specialized feature of 7TM receptors. The very properties that define receptors as such also impart unique protein behaviors to receptors, and these behaviors, in turn, affect drug activity", page 414, column 1, second paragraph. The important features which would help to define the G-protein mediated signal transduction activity and define the genus claimed have not been disclosed in the specification nor prior art, e.g. ligand recognition domains, domains that allosterically transmit the presence of that ligand to an intracellular domain, specific G-protein interaction domain. Further the activity transduced is not disclosed or how it relates structure to function.

Similarly pertaining to nucleic acids which hybridize to the polynucleotide of claim 4, under uncleárly defined hybridization conditions, what is the special technical feature encompassed by said nucleic acids and how do they relate to function.

The claims encompass nucleic acids encoding proteins which are structurally and functionally unrelated to the protein of SEQ ID NO:1. Therefore instant specification

fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. Although claims recite "G-protein coupled receptor", there is no disclosure of the specific activity, encompassed by the GPCR and how it is assayed. The specification nor claims disclose the specific activity of the "orphan receptor" of instant invention nor a description of the conserved regions which are critical to the structure and function of the genus claimed. Further methods of use of claimed GPCR are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections, 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-5, 7-9, 15, 17 and 20-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Young et al (US Patent 5,320,941). Young discloses an isolated polypeptide (SEQ ID NO:2), which has 25.1% query match to SEQ ID NO:1 of instant application (Issued Patents Database, sequence comparison is attached). Young discloses an isolated polynucleotide (SEQ ID NO:1) which has 9.7% query match to SEQ ID NO:3 of instant application (Issued Patents Database, sequence

comparison is attached). The polypeptide and polynucleotide disclosed by Young can be classified as a G protein coupled receptor (based on homology data), which comprises an amino acid sequence substantially identical to the amino acid represented by SEQ ID NO:1, and encodes a polynucleotide comprising a polynucleotide encoding a an amino acid sequence substantially identical to the amino acid represented by SEQ ID NO:1, thereby meeting the limitations of claims 1-5. Young also discloses the production of a recombinant vector (containing substantially identical GPCR), transformant transformed with said recombinant vector and method of producing GPCR comprising culturing said transformant (see Results) thereby meeting the limitation of claims 7-9. Young disclose detectable markers of SEQ ID NO:1 which are complementary in sequence to SEQ ID NO:1, thereby meeting the limitation of claims 20 and 21 (disclose polynucleotide which would hybridize to the polynucleotide of claim 4). Further Young discloses a polypeptide which is substantially identical to the peptide of SEQ ID NO:1 used for transforming cells (column 5). Since disclosed polypeptide must have been stored in a container, therefore it inherently meets the limitation of claim 17 (kit for screening). Young also discloses method of detecting a tumor by contacting a cell (containing a protein substantially identical to the claimed polypeptide of SEQ ID NO:1) with a marker which binds said protein, thereby meeting the limitation of claim 15 (column 5).

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nirmal S. Basi
Art Unit 1646
October 17, 2003

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